

PATENT
454310-5010

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

PAOLETTI, ET AL.

v.

MOSS, ET AL.

Interference 103,399

Administrative Patent Judge
Andrew H. Metz

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on 18 Apr 95

THOMAS J. KUWALSKI, REG. NO. 32,147
Name of Applicant, Assignee or Registered
Representative

Thomas J. Kuwalski
Signature
18 Apr 95
Date of Signature

530 Fifth Avenue
New York, New York 10036

DECLARATION OF ENZO PAOLETTI

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231
BOX INTERFERENCE

Sir:

I, Enzo Paolletti, declare and say that:

1. I executed a Declaration on February 27, 1995

captioned:

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IN THE EUROPEAN PATENT OFFICE

In re: European Patent No.: 0 011 385 B1

European Appln. No.: 83 111976.3

Applicant/Proprietor: United States of America,
as represented by the
Secretary, United States
Department of Commerce

(hereinafter "the European Opposition Declaration").

2. I am advised and therefore believe that a copy of the European Opposition Declaration was filed by Paoletti et al. in the above-captioned Interference. I have read and understood the European Opposition Declaration, hereby incorporate it herein by reference, and, adopt the European Opposition Declaration as testimony in the Interference. I am further advised and therefore believe that the Paoletti Et Al. Motion Under 37 C.F.R. §§ 1.633 And 1.637 For Judgement On Ground That Moss Et. al. Claims Not Patentable To Moss Et Al. ("the Paoletti Motion") cites the Abstracts and presentations of the September 20-23, 1982 Poxvirus-Iridovirus Workshop held at Cold Spring Harbor Laboratory, Cold Spring Harbor, New York ("the September 20-23, 1992 Workshop"), especially the Abstracts at pages 55, 40 and 59 (copy of each attached) and, had a copy of the Abstracts from the September 20-23, 1982 Workshop attached as an Exhibit (Exhibit 4 and included in Exhibit 21). I am also advised and therefore believe that Moss et al. has moved to strike or suppress those Abstracts as allegedly not authenticated. I hereby confirm that

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the Abstracts from the September 20-23, 1982 Workshop attached to the Paoletti Motion and submitted as document D4 in the European Opposition were a true copy of the Abstracts of the September 20-23, 1982 Workshop received by me in the ordinary course of business, at registration for the September 20-23, 1982 Workshop prior to any meetings of the September 20-23, 1982 Workshop and, that since the September 20-23, 1982 Workshop, I have maintained the Abstracts from the September 20-23, 1982 Workshop in my custody and control in the ordinary course of business. Thus, the copy of the Abstracts from the September 20-23, 1982 Workshop attached to the Paoletti Motion and submitted as document D4 in the European Opposition are indeed a genuine, authentic copy of the Abstracts from the September 20-23, 1982 Workshop, publicly distributed at registration for and prior to any meeting of, the September 20-23, 1982 Workshop; and, that the copy of the Abstracts at pages 55, 40 and 59 attached hereto are indeed a genuine, authentic copy of the Abstracts at pages 55, 40 and 59 of the Abstracts from the September 20-23, 1982 Workshop, publicly distributed at registration for and prior to any meeting of, the September 20-23, 1982 Workshop.

3. I further declare that all statements made herein and in the European Opposition Declaration (herein by incorporation by reference) are true and that all statements made on information and belief are believed to be true; and, that

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Exhibit B-3-

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these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon or any Patent or application involved in the Interference.

Date:

April 7, 1995

Enzo Paoletti
Enzo Paoletti

xvirus

-55-

E. Paoletti, Ph.D

POXVIRUSES AS EUKARYOTIC CLONING VECTORS: D. Panicali and E. Paoletti, Center for Laboratories and Research, New York State Department of Health, Albany, NY

Recombinant vaccinia viruses expressing the thymidine kinase gene from Herpes simplex virus (HSV) or the hemagglutinin gene from influenza virus have been constructed and characterized. The foreign gene was first inserted into a non-essential genetic locus of contiguous vaccinia virus DNA sequences cloned in pBR322. These donor chimeric plasmids were introduced as calcium orthophosphate precipitates into eukaryotic tissue culture cells, previously infected with infectious virus. Site specific *in vivo* recombination allowed incorporation of the foreign DNA into the genome of replicating virus. Progeny virus containing the foreign gene were obtained as purified populations by several procedures.

The HSV-TK was incorporated into both the 120 Md prototypic L variant genome, as well as into the S variant, a spontaneous deletion mutant. When rescuing virus was TK⁺, recombinants expressing HSV-TK were selected on TK⁻ cells in the presence of methotrexate. When rescuing virus was TK⁻, recombinant vaccinia viruses expressing HSV-TK were detected by the specific utilization of ¹²⁵I-deoxycytidine (IDC). The endogenous vaccinia TK as well as the TK from a variety of eukaryotic cells failed to utilize IDC as substrate. Recombinant vaccinia viruses containing foreign genetic elements were additionally selected by a novel replica filter plating technique developed in our laboratory. This methodology is independent of expression or biochemical selectability of the foreign gene product and provides a general and rapid procedure for detection and recovery of viral vectors containing foreign genetic elements.

Restriction analysis of progeny recombinant viral DNA demonstrated the insertion and stable integration as a very specific event. Transcriptional analysis of the HSV-TK gene was consistent with the utilization of endogenous vaccinia promoters.

In addition to the foreign genes described above, other foreign DNA sequences have been introduced into recombinant vaccinia viruses including segments of hepatitis B virus. As much as 20 Kbp of foreign DNA have been stably inserted into recombinant vaccinia viruses as an attempt to determine the upper limit of foreign DNA packaging by the virus.

Exhibit B

-40-

NUCLEOTIDE SEQUENCES OF FIVE VACCINIA VIRUS EARLY GENES.

S. Venkatesan, M. Haffey, S. M. Baroudy, and B. Moss.
Laboratory of Biology of Viruses, National Institute of
Allergy and Infectious Diseases, National Institutes of
Health, Bethesda, Maryland 20205.

Regulatory elements discovered as consensus sequences are located upstream of transcriptional initiation sites of eukaryotic and prokaryotic genes. An unusually A-T-rich sequence has been found before a vaccinia virus gene specifying an early 7.5K polypeptide (Venkatesan, Baroudy and Moss, *Cell* 125, 805, 1991). To distinguish common and variable structural features, we have now sequenced five additional early genes. Three of the sequenced genes are located within the 10,000 bp inverted terminal repetition and were found to encode early mRNAs of about 1,000, 500, and 1,050 nucleotides that directed in vitro synthesis of 7.5K, 19K, and 42K polypeptides respectively. Two other early genes are located between 16,000 and 18,000 bp from the left end of the genome and were found to encode mRNAs of about 760 and 880 nucleotides that directed in vitro synthesis of 14K and 32K polypeptides. The sixth gene specifies thymidine kinase and will be presented separately. Previous studies established that none of these mRNAs are spliced and in several cases, the capped ends were shown to be sites of transcriptional initiations. Genome fragments were cloned in plasmid or single-stranded DNA phage vectors and sequenced by the Maxam-Gilbert technique employing a novel "deletion-linker" strategy and/or by the Sanger dideoxynucleotide method. Several approaches including nuclease S1 analysis, primed reverse transcription of mRNAs, cDNA sequencing, and analysis of mRNA ends were used to determine the genomic location of the 5' or 3' ends of the messages. Common features of the early genes include extremely A-T-rich 40 to 60 bp segments immediately upstream of the transcriptional initiation sites, uninterrupted coding sequences, absence of eukaryotic poly(A) signal sequence, and multiple closely spaced 5' and 3' ends of transcripts. Distances between transcriptional and translational initiation sites and translational and transcriptional termination sites were quite variable. In some cases, genes were closely spaced with as little as 10 bp between the end of one and the start of another suggesting overlapping of regulatory sequences for initiation and termination of transcription.

Exhibit B

IDENTIFICATION AND NUCLEOTIDE SEQUENCE OF THE THYMIDINE KINASE GENE OF WILD-TYPE VACCINIA VIRUS AND NONSENSE MUTANTS. Jerry M. Weir, Gyorgy Bajszar, and B. Moss
Laboratory of Biology of Viruses, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland 20205.

The thymidine kinase (TK) gene has been mapped within the HindIII J fragment of vaccinia virus DNA (Weir, Bajszar and Moss, Proc. Natl. Acad. Sci. USA, 79, 1210, 1982). Further investigations revealed that enzymatically active TK was made in reticulocyte lysates programmed with early vaccinia mRNA that hybridized to plasmid recombinants containing either of two adjacent small DNA sub-segments of the viral HindIII J fragment. The map position of an early polypeptide, with a molecular weight of about 19,000 (19K), coincided precisely with that of the TK. The absence of the 19K polypeptide in cell-free translation products of hybridization-selected mRNAs from several TK⁻ mutants provided an independent identification of the TK polypeptide. The small size of the TK polypeptide of vaccinia virus distinguishes it from that of prokaryotes, eukaryotes and herpesvirus. RNAs of 590 and 2,380 nucleotides with 5' coterminal ends represent major and minor forms, respectively, of the TK message. The TK genes of wild-type and 3 putative nonsense mutants were cloned and sequenced by the dideoxynucleotide chain termination method. In each of the mutant DNAs, an extra nucleotide identical to one preceding it had been added. Because of the frameshift, a nonsense codon was introduced downstream. The region preceding the transcriptional initiation site of the TK gene is AT-rich and shares some sequence homology with similar regions of other early genes. Interestingly, the putative transcriptional regulatory region of the TK gene lies within the coding sequence of an adjacent late gene. Moreover, the 3' end of the late transcript overlaps the TK gene.

Exhibit B

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